AR201-13221

October 3, 2001

Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

Attention: Chemical Right-to-Know Program

Re: Cyclohexanol (CAS No. 108-93-0)
Registration No.

Dear Administrator:

Enclosed is the Test Plan for Cyclohexanol submitted for the High Production Volume (HPV) Challenge Program on behalf of the member companies of the IHF Cyclohexanol Committee.

If there are any questions concerning the test plan or robust summary information presented for cyclohexanol, please contact Henry Trochimowicz, Sc.D. D.A.B.T., the technical contact for the Committee, 14 Lamatan Road, Newark, DE 19711; Phone: (302) 239-4725; FAX (302) 239-9618; E-mail: htroch@aol.com.

Sincerely,

Marianne C. Kaschak
Project Coordinator

MK 52535

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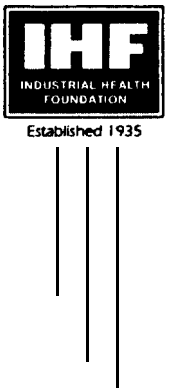

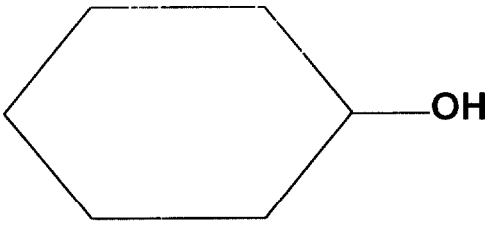

CYCLOHEXANOL

CAS Number 108-93-o

USEPA HPV CHALLENGE PROGRAM SUBMISSION

September 26, 2001

Submitted by:

IHF Committee on HPV Challenge for Cyclohexanol

Members.:

BASF Corporation
DuPont Company
DSM Chemicals North America, inc.
Honeywell International: Inc.
Solutia, Inc.

Prepared by:

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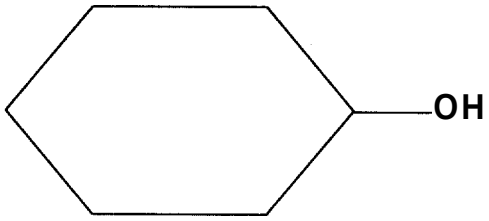

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TESTING PLAN

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EXECUTIVE OVERVIEW

Cyclohexanol is a basic industrial chemical and solvent. It is primarily captively consumed, either isolated or as a mixture, in the production of nylon intermediates (adipic acid and caprolactam). Less than 2% is consumed in other markets such as in the production of cyclohexylamine, and intermediates for plasticizers, rubber chemicals, and selected agricultural chemicals. Total cyclohexanol production in 1998 was estimated at approximately 1240 million pounds. Exposure in the preceding applications is limited by process controls and protective equipment. Environmental releases are primarily limited to vapor released to air at manufacturing sites.

Valid data for cyclohexanol are available for melting and boiling points, vapor pressure, aqueous solubility, octanol-water partitioning, and specific gravity. The data indicate that cyclohexanol will be a solid below about 24° C and liquid at higher ambient temperatures. Based on its vapor pressure, aqueous solubility, and Log P_{ow} value, it will tend to remain in water and only slowly volatilize. Partitioning to soil and sediment and bioaccumulation in aquatic organisms will be low. Assuming equal releases of cyclohexanol to air, water, and soil, Mackay Level III distribution modeling predicted that most would be found in water (50.2%) or soil (47.5%), with the rest in air.

Upon entry into water or soil, the results of an OECD 302 biodegradation study suggest that cyclohexanol will be subject to relatively rapid biodegradation in oxygen-containing environments. Primary and ultimate biodegradation half-lives in water and soil were estimated to be days and weeks, respectively. In the air, hydroxyl radical-mediated photo-oxidation will quickly reduce concentrations with a calculated half-life of less than 15 hours.

Valid acute ecotoxicity data for the freshwater fathead minnow *Pimephales promelas* (96-hr LC50 = 704 mg/l), the invertebrate *Daphnia* **magna** (48-hr EC50 > 500 mg/l), and the green alga *Scenedesmus subspicatus*

(96-hr EC50 = 29 mg/l) indicate that cyclohexanol is practically nontoxic to fish and invertebrates, and slightly toxic to algae.

Acute toxicity to mammals appears to be low-to-moderate as demonstrated by an oral LD50 in rats of about 1550 mg/kg, a 4-hour LC50 in rats >3.6 mg/l (as an aerosol), and a dermal LD50 in rabbits between 500 and 800 mg/kg. Adequate repeated exposure studies have not been conducted on cyclohexanol. Studies of questionable reliability have suggested aspermatogenesis as an adverse effect and no adequate studies to assess developmental toxicity were found. Relative to genetic toxicity potential, in *vitro* studies in bacteria were negative with and without metabolic activation; and *in* vitro cytogenetic assay results using human leukocytes were "equivocal." In an *in* vivo mouse micronucleus study, cyclohexanol was not clastogenic. Toxicokinetic data in animals suggest that cyclohexanol is readily absorbed, subsequently metabolized, and then the parent compound/metabolites are excreted in the urine as glucuronides and sulfates within several days.

With regard to the HPV program, the IHF Committee on Cyclohexanol has determined that no additional testing is needed in the areas of "Physicochemical Properties", and "Ecotoxicity." Relative to "Environmental Fate", an existing biodegradation study and modeling data on photodegradation and transport and distribution in the environment are adequate to meet HPV requirements. However, additional testing for water stability (OECD 111, for example) is needed. Relative to mammalian toxicity, acute toxicity data and genotoxicity data are adequate to meet HPV requirements.

Overall, cyclohexanol does not appear to represent an unacceptable risk to human health or the environment. Under the EPA HPV Challenge Program, cyclohexanol was evaluated and data gaps were identified for water stability, repeated exposure toxicity and reproductive/developmental toxicity. In deciding what animal tests/studies to conduct, the IHF Committee on Cyclohexanol considered the animal usage required and recommends a rat 90-day inhalation toxicity study. If reproductive organ effects are seen in that 90-day study, an inhalation one-generation reproduction study will be conducted. If no reproductive

organ effects are seen in the 90-day study, then an inhalation developmental toxicity will be performed. By keeping the number of tests and the number of animals in those tests to a minimum, the Committee feels that animal welfare concerns have been appropriately addressed. Appropriate studies to meet the HPV requirements will reference OECD Guidelines and will be conducted starting in the first quarter of 2002 and take about two years to complete.

TESTING PLAN AND RATIONALE

TESTING PLAN IN TABULAR FORMAT

Cyclohexanol CAS No. 108-93-o	Information Available?	OECD Study?	GLP Study?	Other Study?	Estimation Method?	Acceptable?	Testing Recommended?	Comments
HPV Endpoint								
Physical/Chemical Properties								
Melting Point	Y	N	N	N	N	Y	N	
Boiling Point	Y	N	N	N	N	Y	N	
Vapor Pressure	Y	N	N	Y	N	Y	N	
Partition Coefficient	Y	Y	N	N	N	Y	N	
Water Solubility	Y	N	N	N	N	Y	N	
Environmental Fate								
Photodegradation	Y	N	N	N	Y	Y	N	
Water Stability	Y	N	N	N	N	N	Y	
Transport	Y	N	N	N	Y	Y	N	
Biodegradation	Y	Y	N	N	N	Y	N	
Ecotoxicity								
96-Hour Fish	Y	N	N	N	N	Y	N	
48-Hour Invertebrate	Y	Y	N	N	N	Y	N	
72-Hour Algae	Y	Y	N	N	N	Y	N	
MammalianToxicity								
Acute Toxicity	Y	N	N	N	N	Y	N	
Repeated Dose	Y	N	N	Y	N	N	Y	
Genotoxicity (Point Mutation)	Y	N	N	Y	N	Y	N	
Genotoxicity (Chromosome Aberration)	Y	Y	Y	N	N	Y	N	
Reproductive Toxicity	Y	N	N	Y	N	N	Y/N	Depends on 90-Day Results
Developmental Toxicity	N	N	N	N	N	N	Y/N	Depends on 90-Day Results

INTRODUCTION

Cyclohexanol, CAS No. 108-93-0, is an alcohol used primarily in the production of nylon intermediates (adipic acid and caprolactam); less than 2% is consumed in markets other than nylon.

Since cyclohexanol is a liquid of low volatility with a vapor pressure of 1 mmHg @ 20° C, little vapor exposure occurs. In the industrial setting, exposures are well controlled and air concentrations are kept at least an order of magnitude below the current OSHA PEL and ACGIH TLV® of 50 ppm (8-hour TWA) under normal operating conditions. Since cyclohexanol can be absorbed through the skin in toxicologically significant amounts, the current ACGIH TLV® also carries a "SKIN Notation." As a result, dermal exposure to cyclohexanol is kept to a minimum in the workplace. Since there are few sites of manufacture, the number of potentially-exposed workers is also small.

Various studies have been conducted on the fate and toxicity of cyclohexanol. These studies are reviewed with comments describing whether or not they meet the requirements of the USEPA High Production Volume (HPV) program. Robust summaries, using a SIDS format, have been prepared for key and some supporting studies and are included in a separate document; other supporting studies are referenced in this document.

PHYSICAL-CHEMICAL DATA

Physical/chemical properties for cyclohexanol are available from the literature and manufacturing company sources.

Melting Point	24" C (1)
Boiling Point	161" C (2)
Vapor Pressure	1.0 mm Hg @ 20° C (1)
Partition Coefficient	$Log_{10} P_{ow}$ = 1.25 @ 25°C (3)
Water Solubility	3.6 wt% @ 20°C (2)

Cyclohexanol is a 6-carbon ring with anOH group on Cl. It is characterized as colorless needles at temperatures below its melting point (1) of 24ºC or as a viscous hygroscopic liquid with a camphor-like odor above its melting point. Its boiling point is 161º C (2) and its specific gravity is 0.945, nearly that of water. Data for cyclohexanol are available for vapor pressure, aqueous solubility, and octanol-water partitioning. Based on a measured vapor pressure of 0.8 mm Hg (25ºC), and aqueous solubility of about 36,000 mg/L (2), calculated from a measured log Kow 1.23, it will tend to remain in water and only slowly volatilize. A Henry's Law constant of 2.5 E-6 atm-m3/mol was calculated from vapor pressure and water solubility. Using these data, volatilization from a model stream and lake were calculated to have half-lives of 5.6 and 64 days, respectively. Partitioning to soil and sediment and bioaccumulation in aquatic organisms will be low, as indicated by a calculated Koc value of 8 L/kg and bioconcentration factor of 2 L/kg (both based on a log Kow of 1.23). Assuming equal releases of cyclohexanol to air, water, and soil, Mackay Level III

distribution modeling predicted that most would be found in water (50.2%) or soil (47.5%), with most of the rest in air (2.25%).

Recommendation: No additional studies are needed to fulfill the HPV required endpoints for physical/chemical properties.

ENVIRONMENTAL FATE AND PATHWAYS

Atmospheric photo-oxidation is an important removal process for cyclohexanol. Using the EPA-developed model AOPWIN (part of EPIWIN), a secondary rate constant for hydroxyl radical mediated atmospheric photo-oxidation was calculated to be 17.48 E-12 cm /molecule-set for cyclohexanol. Using the standard assumptions of 1.5 E+6 hydroxyl radicals per cubic centimeter, and 12 hr/day of daylight, a pseudo first-order half-life of 0.61 days (14.7 hours) was calculated. No data for hydrolysis is available and EPIWIN models cannot estimate hydrolysis rates for compounds with a structure like cyclohexanol.

Biodegradation is an important removal process for cyclohexanol. The biodegradation of cyclohexanol was determined by measuring consumption of dissolved organic carbon (DOC). The study (4) employed OECD method 302, Zahn-Wellens test. The 6-day study was initiated using non-adapted activated sludge as microbial seed. DOC was measured at 3 hours, 1 day, 4 days, and 6 days. At 3 hours, 11% DOC removal was reported. On days 1, 4, and 6 of the test, 45%, 98% and 98% DOC removal were achieved. Cyclohexanol is considered inherently biodegradable and the data suggest that it will be subject to relatively rapid biodegradation in oxygen-containing environments. The biodegradability of cyclohexanol is supported by results obtained using BIOWIN v4.00 (of the EPIWIN models), which estimated primary and ultimate biodegradation half-lives in water and soil of days and weeks, respectively.

Recommendation: The preceding biodegradation study (OECD 302B) and the modeling data for photodegradation (AOPWIN) and transport and distribution (Mackay Level III) are adequate to meet SIDS/HPV requirements. Cyclohexanol is readily biodegradable; thus, this information supports not measuring stability in water (hydrolysis). The EPIWIN model cannot estimate hydrolysis rates for a chemical with a structure like cyclohexanol. Therefore, we propose to conduct a study (OECD 111, for example) to measure the stability (hydrolysis) of cyclohexanol in water.

ECOTOXICITY

Acute aquatic toxicity data are available for cyclohexanol in fish, invertebrates and algae. An EPA sponsored study (5,6) was performed with the freshwater fathead minnow *Pimephales promelas.* The study followed EPA-developed flo-through guidelines on ecotoxicity testing and was deemed valid. The fathead minnow 96-hr LC50 based on survival was 704 mg/L. A study (7) with the pelagic aquatic invertebrate *Daphnia magna* was performed using OECD method 202. No effects were observed at the highest concentration tested, 500 mg/L, so the 48-hr EC50 was >500 mg/L. A static study (8) with the green alga *Scenedesmus subspicatus* was also performed according to OECD method 201, which measures the inhibitory effect on cell multiplication, a measure of growth rate. Both the 72-h EC50 and the 96-hr EC50 values were 29 mg/L.

Recommendation: No additional testing is recommended based on available data. The preceding ecotoxicity studies do not suggest that cyclohexanol represents a major concern for aquatic environmental species,

MAMMALIAN TOXICITY

A. Acute Toxicity

The acute oral toxicity of cyclohexanol was determined in male SD rats using a method consistent with OECD Test Guideline 401. Doses of 1000, 1260, 1580, 2000, 2510 and 3160 mg/kg were used. No mortality occurred at 1000 or 1260 mg/kg. The LD50 was reported to be 1550 mg/kg (1390-I 710 mg/kg CL) (9). This low order of toxicity is supported by an older acute oral toxicity study in Car-worth-Wistar rats with a reported LD50 of 2060 mg/kg for cyclohexanol (10).

An adequate inhalation toxicity study using one exposure level in SD rats also suggests a low order of toxicity. Ten male and 10 female rats were exposed to a cyclohexanol aerosol for 4 hours at an analytical concentration of 3.63 mg/l and were observed up to 14 days post-exposure. No rats died and clinical observations, body weight changes and gross autopsy results were unremarkable (11).

In a dermal absorption toxicity study, using a method consistent with OECD Test Guideline 402, cyclohexanol was applied undiluted to the skin of rabbits for 24 hours at 7 doses ranging from 316 to 5010 mg/kg. The dermal LD50 was reported as >501 <794 mg/kg, values reflecting a slightly greater toxicity by the dermal route compared to the oral route. These data also suggest that cyclohexanol can be absorbed through the skin in toxicologically significant amounts (12). As a result, the current ACGIH TLV® of 50 ppm (8-hr TWA) for cyclohexanol also has a 'SKIN' notation.

Recommendation: The oral toxicity studies, as well as supporting studies by inhalation and dermal routes, suggest that cyclohexanol has a relatively low

order of acute toxicity. These studies adequately fulfill the HPV acute toxicity requirement and no additional testing is recommended.

B. **Repeated Dose Toxicity**

The data available to assess the repeated exposure toxicity of cyclohexanol are inadequate to meet the HPV requirements for this endpoint. Limited repeated exposure studies have been conducted by the oral route (13-17), the inhalation route (18-21), and the dermal route (18-22). From these studies, it appears that the major adverse effects of repeated exposure to cyclohexanol are CNS effects, liver and kidney damage, and mucous membrane irritation.

Recommendation: The IHF Committee on Cyclohexanol recommends that a 90-day inhalation toxicity study in rats (OECD Guideline No. 413) be conducted to satisfy this HPV endpoint. This study will include a recovery group and complete histopathological examination of tissues with special emphasis on testes and ovaries. In addition, recovery groups will be included to assess the reversibility of any lesion seen after 90 days of exposure. Such a study will provide sufficient information to adequately assess repeated exposure toxicity potential. In addition, it will provide some guidance in deciding whether to conduct studies to assess the reproductive toxicity (See Section D) and/or the developmental toxicity (See Section E) potential of cyclohexanol.

C. Genotoxicity

In vitro studies conducted on cyclohexanol have shown negative or ambiguous results. In an adequate *Salmonella typhimurium* reverse mutation assay (23), four strains (TA 98, TA1535, TA 1537 and TA 1538) were exposed to cyclohexanol at concentrations up to 15,000 g/p late. Two replicates were used at each concentration and all tests were performed with and without metabolic activation. No evidence of mutagenicity was seen in

this study. Three other *in vitro* point mutation assays using *Salmonella typhimurium* were also conducted on cyclohexanol. In two of these studies (24,25), there was no evidence of mutagenicity but details were limited. In a third study (26), cyclohexanol tested at 3300 and 9100 g/plate, with and without activation, produced less than a two-fold increase in revertants, a result that would be considered negative by today's standards. In one *in vitro,* non-bacterial assay (27) measuring chromosomal aberration, human leukocytes were tested at concentrations as high as 0.01 moles/l without metabolic activation. Cyclohexanol reportedly induced achromatic regions, breaks and deletions in chromosomes. However, this study used a non-validated protocol and technical details were very limited.

One *in vivo* genotoxicity study (28), considered "valid without restrictions", was conducted by BASF on cyclohexanol using a mouse micronucleus assay. Male and female mice were dosed by oral gavage at concentrations of 500,1000 and 1500 mg/kg, sacrificed 16, 24 and 48 hours later, and bone marrow was examined. Cyclohexanol produced no chromosome-damaging (clastogenic) effects and did not impair chromosome distribution in mitosis. In one other limited *in vivo* gene mutation assay *(29)* in *Drosophila melanogaster,* results were negative.

Recommendation: No additional testing is required. The HPV requirement for genetic testing has been met by the preceding *in vitro* and *in vivo* studies sensitive to both point mutations and chromosome aberrations. From these studies, the overall weight of evidence suggests a lack of genotoxic activity for cyclohexanol.

D. Reproductive Toxicity

A few limited studies, involving evaluation of the testis, have been conducted but are not adequate to meet HPV requirements.

In one study (30), 20 adult male gerbils and 20 male rats were subcutaneously injected with 15 mg cyclohexanol/kg/day for a period of 21 and 37 days, respectively. A significant reduction in the weights of the testes, epididymides, seminal vesicles and ventral prostate was detected. In addition, spermatogenesis in both species was arrested. Recovery was not investigated.

In another study, (31), groups of 15 male rabbits received 25 mg cyclohexanol/kg/day by gavage for a period of 40 days. One group was allowed a 70-day recovery period following cessation of cyclohexanol administration. A significant reduction in the weights of the testis and epididymides was observed. Additionally, marked degenerative changes were noted upon microscopic examination of the testes. These changes were consistent with those previously described for the gerbil and the rat. Normal spermatogenesis was seen after 70 days following cessation of cyclohexanol treatment. The organ weights were also comparable to the controls. In a third study (14), male rats were given 455 mg cyclohexanol/kg/day by gastric intubation for 7 days. Cyclohexanol increased liver size and stimulated certain parameters of hepatic xenobiotic metabolism in the rat but had no effect on testis weight. Other studies cited under “Repeated Dose Toxicity” (See Section B) make no mention that gonadal tissue was ever examined histopathologically.

Recommendation: If adverse effects on gonads (sperm damage, for example) are observed in the proposed 90-day rat inhalation study (Section B), a one-generation rat inhalation reproduction study (OECD No.415) will be conducted on cyclohexanol to assess functional effects on fertility/reproductive performance.

E. Developmental Toxicity

No adequate studies were found to assess the developmental toxicity potential of cyclohexanol.

Recommendation: If no adverse gonadal effects are seen in our proposed 90-day rat inhalation study (Section B), an inhalation teratology study (OECD No. 414) in rats will be conducted to fulfill the HPV reproductive/developmental toxicity requirement.

F. Toxicokinetics

Limited data exist on specific aspects of toxicokinetics - namely, metabolism and excretion. The major occupational exposure routes for cyclohexanol are inhalation and the skin. Several animal studies dealing with absorption, metabolism and excretion are subsequently discussed.

Little quantitative data on absorption and distribution of cyclohexanol in animals were found. The dermal LD50 in rabbits was reported to be between 501 and 794 mg/kg, suggesting that cyclohexanol can be absorbed through the skin in toxicologically significant amounts (12). Cyclohexanol has also been reported to facilitate the penetration of externally applied drugs through the skin (32), but no recent confirmatory studies were found.

The literature suggests that cyclohexanol is a substrate for alcohol dehydrogenase (ADH), has a stronger affinity for the enzyme than ethanol, and would competitively inhibit the oxidation of ethanol (25, 33-35). Cyclohexanol also interacts with cytochrome P450 (36-37). In one recent study (17), cyclohexanol remarkably enlarged the mitochondria in the hepatocytes of rats, but only after the solvent was given for 30 days.

In studies on dogs, results have been equivocal. One study (18) reported the presence of glucuronides in the urine of one dog after oral administration of

cyclohexanol. However, other investigators (13, 38) could not detect any cyclohexanol, conjugated or free, or metabolites in the urine of a dog after subcutaneous administration for 6 days or after oral administration for 7 days. Data on rabbits appears to be more consistent. Following oral or inhalation administration to rabbits, cyclohexanol was excreted in the urine in conjugation with sulfuric and glucuronic acids. At an oral dose of 1200 mg/kg, 4550% was conjugated with glucuronic acid, accompanied by an increased percentage of inorganic sulfates. Cyclohexanone as a possible oxidation product of cyclohexanol was not found in the urine (22). In another study (39), rabbits given 250 mg/kg of labeled cyclohexanol excreted 58-60% of the dose in the urine as glucuronides and 12% of the dose as trans-cyclohexane-1,2-diol glucuronide. About 71% of the radioactivity was excreted in the urine in 48 hours

From the preceding animal studies, it is evident that cyclohexanol can be absorbed by all three major routes of administration. Most absorbed cyclohexanol is metabolized and subsequently excreted as glucuronide and sulfate conjugates. One investigator (22) calculated a half-life of about 12 hours for these metabolites.

CONCLUSIONS

Under the EPA HPV Challenge Program, adequate data to meet HPV requirements are available for cyclohexanol relative to Physical/Chemical Properties, Environmental Fate and Pathways, (except for water stability), Ecotoxicity, Acute Toxicity and Genotoxicity. A study on water stability (hydrolysis) will be conducted. A rat 90-day inhalation toxicity study with a recovery phase will also be conducted on cyclohexanol. Depending on results from this study, either a one-generation inhalation reproduction study or an inhalation developmental toxicity study in rats will be conducted. The preceding proposed studies, coupled with toxicity and environmental data already

available, should adequately characterize cyclohexanol relative to HPV requirements.

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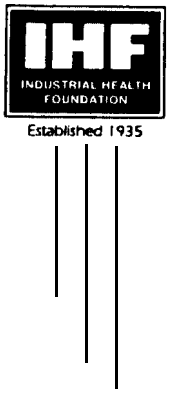

TIER 1 SCREENING SIDS DOSSIER
ON THE HPV PHASE...CHEMICAL

CYCLOHEXANOL.

CAS NO. 108-93-O

September 26, 2001

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TIER 1 SCREENING SIDS DOSSIER
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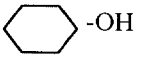
CONTENTS

SIDS PROFILE

DATE: September 26,200 1

1.01 A.	CAS No.	108-93-0
1.01 C.	CHEMICAL NAME	CYCLOHEXANOL
1.01 D.	CAS DESCRIPTOR	Not applicable
1.01 G.	FORMULA & STRUCTURE	$C_6H_{12}0$ 
1.5	QUANTITY	1240 million pounds for 1998
1.7	USE PATTERN	Mainly used in the production of adipic acid and cyclohexylamine. Also used as an intermediate for pesticides, plasticizers, rubber chemicals, and pharmaceuticals; very limited use as a special process solvent.
1.9	SOURCES AND LEVELS OF EXPOSURE	Process leaks during manufacture of cyclohexanol or conversion to other chemicals such as caprolactam, adipic acid and cyclohexylamine would give rise to some vapor concentrations which may affect exposed personnel. There is also a low probability of skin contact for which maintenance workers would be primarily affected.
TEST PLAN JUSTIFICATION/ ISSUES FOR DISCUSSION	SIDS testing required: Repeated exposure study and, depending on results, either a one-generation reproduction study or a developmental toxicity study; also, water stability (hydrolysis) will be measured.	

Tier 1

SIDS SUMMARY

DATE: September 26,200 1

CAS NO: 108-93-o		Information	OECD Study	GLP	Other Study	Estimation Method	Acceptable	SIDS Testing Required
STUDY		Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	YIN
PHYSICAL-CHEMICAL DATA								
2.1	Melting Point	Y	N	N			Y	N
2.2	Boiling Point	Y	N	N			Y	N
2.3	Density	Y	N	N			Y	N
2.4	Vapor Pressure	Y	N	N			Y	N
2.5	Partition Coefficient	Y	Y	N			Y	N
2.6	a. Water Solubility b. PH and pKa Values	Y					Y	N
2.7	Flash Point	Y						
2.8	Flammability	Y						
2.12	Oxidation: Reduction Potential	N						
2.13	Adsorption/Desorption to Soil	Y						

ENVIRONMENTAL FATE and PATHWAY								
3.1.1	Photodegradation	Y	N		Y	Y	Y	N
3.1.2	Stability in water	Y/N			Y	N	N	Y
3.3	Transport and Distribution	Y	N			Y	Y	N
3.5	Biodegradation	Y	Y			N	Y	N
ECOTOXICITY								
4.1	Acute Toxicity to Fish[1]	Y	N	N			Y	N
4.2	Acute Toxicity to Daphnia[1]	Y	Y	N			Y	N
4.3	Toxicity to Algae[1]	Y	Y	N			Y	N
TOXICITY								
5.1	Acute Toxicity							
5.1.1	Acute Oral	Y	N	N			Y	N
5.1.2	Acute Inhalation	Y	N	N			Y	N
5.1.3	Acute Dermal	Y	N	N			Y	N
5.4	Repeated Dose (General)	N						Y
5.5	Genetic Toxicity *in vitro* ▪ Gene mutation ▪ Chromosomal aberration	Y	N	N			Y	N
5.6	Genetic Toxicity in *vivo*	Y	N	Y			Y	N
5.7	Reproduction Toxicity	Y	N	N	Y		N	Y*
5.8	Developmental Toxicity/Teratogenicity	N	N	N			N	Y*

*Depending on results from the 90-day study, either a one-generation reproduction study or a developmental toxicity study will be conducted.

1. GENERAL INFORMATION

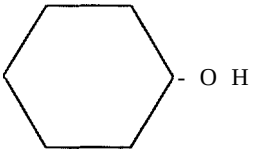
1.01 SUBSTANCE INFORMATION

A. CAS-Number 108-93-0

C. OECD Name Cyclohexanol

D. CAS Descriptor Not applicable

G. Structural Formula $C_6H_{11}OH$ (smiles code)



1.5 QUANTITY

Remarks: Cyclohexanol (and cyclohexanone) is primarily consumed either isolated or as a mixture, in the production of adipic acid and caprolactam. According to company confidential data, approximately 1240 million pounds of cyclohexanol was produced in 1998. Less than 2% of this has typically been sold for use in other markets. The manufacturing process starts with either cyclohexane or phenol. (Stahl, W.F., Chemical Economics Handbook, SRI International – CEN Data Summary, Cyclohexanol and Cyclohexanone – United States, May 1998). According to that document, the merchant market for cyclohexanol was 27 million pounds in 1996 with over half (15 million pounds) used in the production of cyclohexylamine. More recently however, the primary manufacturers of cyclohexylamine have apparently switched to aniline as the raw material of choice making the market for cyclohexanol even less on a current basis.

Reference: Industrial Health Foundation, Pittsburgh, PA, June 18, 200 1

1.7 USE PATTERN

Remarks: Most of the cyclohexanol produced (-98%) is used in the production of adipic acid and caprolactam during the manufacture of nylon polymer. Other uses include the following:

a. Intermediate for agricultural chemicals (pesticides).
b. Intermediate for plasticizers
c. Intermediate for rubber chemicals.
d. Intermediate for pharmaceuticals.

Most of these uses involve further processing. Exposure to cyclohexanol in chemical processing is generally low because of the nature of the closed systems employed. Exposure of those using cyclohexanol as a chemical intermediate is expected to be similar to those found in manufacturing.

A limited amount of cyclohexanol is used as a solvent [primarily in special processes). The high melting and boiling points and low vapor pressure restrict its use as a general solvent. In these applications, appropriate handling guides (OSHA PEL, ACGIH TLV® or equivalent) have been established to assure safe handling. The low vapor pressure (essentially a solid at room temperature) helps in reducing the potential for human exposure by inhalation.

1.9 SOURCES OF EXPOSURE

Process leaks during manufacture of cyclohexanol or conversion to other chemicals such as caprolactam, adipic acid and cyclohexylamine would give rise to some vapor concentrations which may affect exposed personnel. There is also a low probability of skin contact for which maintenance workers would be primarily affected.

2.0 PHYSICAL/CHEMICAL DATA

2.1 Melting Point

Value:	24^0C
Decomposition:	No Data
Sublimation:	No Data
Method:	No Data
GLP:	Yes[]No[]?[X]
Remarks:	
Reliability:	[4] Not assignable because limited study information was available
Reference:	BASF/AG Sicherheitsdatenblatt (MSDS), Cyclohexanol (6/22/93), Ludwigshafen, Germany

2.2 Boiling Point

	Value:	161.1°C
	Pressure:	at 101.3 kPa
	Decomposition:	No Data
	Method:	No Data
	GLP:	Yes [ ] No [ ] ? [X]
	Remarks:	No additional data
	Reliability:	[4] Not assignable because limited study information was available
	Reference:	Budavari, S.(ed.), The Merck Index, 11TH Ed.,Rahway, NJ: Merck & Co., Inc., Whitehouse Station, NJ, 1989, p.426.

2.3 Density

	Type:	Bulk Density [ ] Density [ ] Relative Density [X]
	Value:	**0.9624**
	Temperature:	20/4^{0}C
	Method:	No Data
	GLP:	Yes [ ] No [ ] ? [X]
	Remarks:	No additional data
	Reliability:	[4] Not assignable because limited study information was available
	Reference:	Lide, D.R.(ed.), CRC Handbook of Chemistry and Physics, 75th Ed., Boca Raton (FL), CRC Press Inc., 1994-1995, pp. 3 – 125.

2.4 Vapor Pressure

	Value:	1.33 kPa (1.0 mmHg)
	Temperature:	**20°C**
	Method:	calculated [ ] measured [ ]
	GLP:	Yes [ ] No [ ] ? [X]
	Remarks:	No additional data
	Reliability:	[4] Not assignable because limited study information was available
	Reference:	BASG/AG Sicherheitsdatenblatt (MSDS), Cyclohexanol (6/22/93), Ludwigshafen, Germany.

2.5 Partition Coefficient $\log_{10}$Pow

	$\log_{10}$Pow:	**1.25**
	Temperature:	25^{0}C

Method:	calculated [ ] measured [X] according to OECD Guideline 107- "Partition Coefficient (n-octanol/water; Flask-Shaking method
Result:	Evaluation of isolated component: Cyclohexanol log Pow=1 .25 Cyclohexanone log Pow= 0.86
Remarks:	Test conditions: 25 ml octanol and 25 ml distilled H_2O, stationary phase: Megabore-capillary (DB-17), thickness of film: 1.0 mm, diameter: 0.53 mm, length: 30 m, stove temperature: 60-l 60°C, detector temperature: 250°C, sampler temperature: 250°C, carrier gas: N_2, columns heat pressure: 1 .5 bar (absolute), total gas flow: 165 ml/min, injection amount: 2.0 ml, instrument: HP 5890 with auto sampler, detector: flame ionization detector average from 3 measurements
Test Substance:	test substance= Anolon™ mixture: 53.6% Cyclohexanol 42.0% Cyclohexanone 4.4% other
GLP:	Yes[]No[ ]?[X]
Reliability:	(2) valid with restrictions Discrepancy between documented test parameters and standard methods, but scientifically, acceptable
Reference:	BASF AG Laboratory of Analytical Chemistry. Unpublished Data (J.Nr.101745/01), 7/12/1988.

2.6 Water Solubility

Value:	**3.6** wt%
Temperature:	20°C
Description:	[ ] Of very high solubility [ ] Of high solubility [ ] Soluble [X] Slightly Soluble [ ] Of very low solubility [ ] Not soluble
Method:	No information
GLP:	Yes [ ] No [ ] ? [X]
Remarks:	No additional data
Reliability:	[4] Not assignable because limited study information was available
Reference:	Budavari, S. (ed.), The Merck Index, 1 1th Ed., Rahway, NJ; Merck & Co., Inc., Whitehouse Station, NJ, 1989, p.426.

2.7 Flash Point: 68°C (SF Closed Cup)

2.8 Auto Flammability: 285°C (DIN 5 1794)

2.12 Oxidation:Reduction Potential-No Data

2.13 Adsorption/Desorption to Soil

Method: Syracuse Research Corporation Model

Remarks: Cyclohexanol is slightly soluble in water with a value of 3.6 wt% at 20°C. If released to soil, it is expected to exhibit high-to-very-high mobility in soil. It may leach through soil to groundwater. It will not hydrolyze in moist soil, but it may be subject to volatilization from surface soil based upon estimated rates for its volatilization from water. It may be subject to biodegradation in soil based on results seen in laboratory aqueous screening tests.

3.0 ENVIRONMENTAL FATE AND PATHWAYS

3.1 Stability

3.1.1 Photodegradation

A. Method

Type: Air [X] Water [ ] Soil [ ] other [ ]

Rate Constant: 17.48 E- 12 (cm^3/molecules-sec)

Method: Calculated using AOPWIN v1.90 SAR Model

Remarks: Atmospheric photo-oxidation potential was estimated using the submodel AOPWIN (Meylan and Howard, 2000a). the estimation methods employed by AOPWIN are based on the SAR methods developed by Dr. Roger Atkinson et al. that rely on structural features of the subject chemical. The model calculates a second-order half-life with units of cm^3/molecules-sec. Photodegradation based on atmospheric photo-oxidation is based on the second order rate of reaction with hydroxyl radicals (HO.), ($k2_{phot}$ with units ot cm^3/molecules-sec). Default AOPWIN assumptions for calculation of first-order half-lives include an HO· concentration of 1.5 E+6 molecules/cm^3 and 12 hours of daylight each day. Pseudo first-order half-lives ($t_{1/2}$) were then calculated as follows: $t_{1/2} = 0.693 / k2_{phot} \times HO\cdot \times 12\text{-hr} / 24\text{-hr}$.

For cyclohexanol, the $k2_{phot}$ value was calculated to be 17.48 E-12 cm^3/molecules-sec and the resulting half-life was $t_{1/2}$ = 0.612 days or 14.7 hours.

Reliability: [2] Valid with Restrictions

Reference: Meylan, W. and P.H.Howard. 2000a. User's Guide for AOPWIN, Version I .9, Syracuse Research Corporation, North Syracuse, NY, March. 2000.

3.1.2 Stability in Water

No data for water stability (hydrolysis) is available and EPIWIN models cannot estimate hydrolysis rates for a compound with a structure like cyclohexanol; however cyclohexanol is fairly biodegradable and that information supports not measuring stability in water (hydrolysis).

3.2 Transport and Distribution between Environmental Compartments Including Estimated Environmental Concentrations and Distribution Pathway

Method:	Calculation according to Mackay, Level 111, fugacity-based models obtained from Trent University's Modeling Center. Specific model: Equilibrium Concentration Model (EQC) Level 3 Model, Version 1.01.
Remarks:	Default values were assumed for environmental compartment descriptions, dimensions, and properties, advective and dispersive properties. Chemical specific parameters were: molecular weight (100. 16 g/mol), Henry's Law Constant (4.44 E-6 atm-m3/mol), vapor pressure (0.65 mm Hg), log Kow (I .23), air half-life (14.7 hr), water and soil half-lives (360 hr), sediment half-life (1440 hr), and equal loadings to air, water, and soil.
Results	Distribution was as follows: Air (2.25%) Water (50.2%) Soil (47.5%) Sediment (<0.1%)
Reliability:	[2] valid without restriction
Reference:	Meylan, W. and P.H. Howard. 2000a. User's Guide for AOPWIN, Version 1.9 Syracuse Research Corporation. North Syracuse, NY. March, 2000.
	Mackay, D. et al. 1996a. Assessing the fate of new and existing chemicals: a live-stage process. *Environ. Toxicol. Chem.* 15(9): *16* 18- *1626.*
	Mackay, D. et al. 1996b. Evaluating the environmental fate of a variety of types of chemicals using the EQC model. Environ. *Toxicol. Chem.* 15(9): 1627-1637.

3.5 Biodegradation

Type:	aerobic [X] anaerobic [ ]
Inoculum:	non-adapted
Concentration of the chemical:	398 mg/l related to dissolved organic carbon (DOC)
Medium:	activated sludge
Degradation:	= 98% after 6 days
Kinetics:	I 1% after 3 hours 45% after I day 98% after 4 days
Method:	OECD Guideline 302B. "Inherent biodegradability: Modified Zahn-Wellens Test"

Test Substance:	as prescribed by 1.1-1.4
Results:	Concentration : 13 1 mg/l DOC = 398 mg/l, AOX < 1 mg/l Elimination after 3 hours : 370 mg/l DOC after 6 days: 24 mg/l
Test Conditions:	steam solution: DOC = 3060 mg/l AOX < 3 mg/1, pH = 7.7 value = 300 ml, inoculumn = 150 mg/l
GLP:	Yes [ ] No [ ] ? [X]
Reliability:	[2] valid with restrictions
Reference:	BASF AG, unpublished data. LGU 87-758. 2.2/6187, 10/8/1990

4.0 ECOTOXICOLOGICAL DATA

4.1 Acute toxicity to Fish

A. Preferred Result

Type of Test:	static [ ] semi-static [ ] flow-through [X] other [ ]
Species/Strain:	Pimephales promelas (fathead minnow) from Environmental Research Laboratory, Diluth culture
Exposure period:	96 hours
Results:	96-hour LC50 = 704 mg/l (CL not relevant)
Analytical monitoring:	Yes
Method:	Test method of the USEPA Committee on Methods for Toxicity (1975). Approximately 25 fish, about 29 days old, were exposed for 96 hours to nominal cyclohexanol concentrations of 0, 133, 222, 369, 6 16 and 1026 mg/L; each concentration was run in duplicate. Analytically measured concentrations for each group (and its replicate) were: <0.7 (<0.7), 120 (124), 183 (185), 304 (310), 532 (533) and 942 (952) mg/L. During the exposure period, the average temperature of the test medium was 24.4 °C ± 0.72 °C (mean ± ISD).
Test Substance:	Purity 99%
GLP:	Yes[ ] No [ ]? [X]
Remarks:	At 96 hours, 100% mortality was observed at the highest dose level. No mortality was seen at other doses or in the control group at 96 hours. Affected fish lost equilibrium prior to death. Fish in the tank did not school after 30 hours of exposure. The 96-hr LC50 was calculate using the trimmed Spearman-Karber method on a PDP 1 1/70 computer.
Reliability:	[2] valid with restrictions
References	Brooke, L.T., et al. Acute Toxicity of Organic Chemicals to Fathead Minnows, Vol. 1 Center for Lake Superior Environmental Studies, University of Wisconsin, 1982.

B. Supporting Data

The preceding study and 9 to I 1 other freshwater fish studies have been conducted on cyclohexanol and are reported in USEPA's ECOTOX Report (November 27, 2000) All show the same Low order of acute toxicity to freshwater fish.

4.2 Acute Toxicity to Invertebrates

Type of Test:	static [ ] semi-static [ ] flow-through [ ] other [ ] ? [X]
Species:	*Daphnia magna*
Exposure period:	48 hours
Results:	EC_0 = 250 mg/l EC_{50} >500mg/l EC_{100} >500 mg/l
Analytical monitoring:	Yes [ ] No [X]
Method:	Directive 84/449/EEC, C.2 "Acute Toxicity for Daphnia" (1998)
Test Substance:	Cyclohexanol ($C_6H_{11}OH$), produced at BASF AG in Ludwigshafen (batch number: B7/11/87, commercial product) with: purity of > 99% molecular weight: 100.16 g/mol color: colorless water solubility: 40 g/l (20° C) homogeneity: homogeneous
GLP:	Yes [ ] No [ ] ? [X]
Remarks:	Test water has a pH of 7.9 a total hardness of 2.55 mmole/l, as alkalinity up top 4.3 of 0.85 mmole/l, a conductivity of 550-650 ms/cm, a test temperature of 292-294°K, and a oxygen content of > 2 mg/l.
Reliability:	[2] Valid with restrictions
Reference:	BASF AG, Department of Ecology, Unpublished Data (111 1/87), 1/1 511988.

4.3 ACUTE TOXICITY TO AQUATIC PLANTS (e.g. Algae)

Type of test:	static [X] semi-static [ ] flow-through [ ] other [ ]
Species:	*Scenedesmus subspicatus* (Algae)
Exposure period:	72 hours
Endpoint:	growth rate
Results:	72-hr EC20 = 0.11 mg/l 72-hr EC50 = 29.2 mg/l 96-hr EC20 = 0.22 mg/l 96-hr EC50 = 29 mg/l 96-hr EC90 = 470 mg/l
Analytical monitoring:	Yes [ ] No [X]

Method: DIN 38412, Part 9, "Determination of inhibitory effection on cell multiplication" (1988)

Test substance: Cyclohexanol ($C_6H_{11}OH$), produced at BASF AG in Ludwigshafen (batch number: B7/11/87, commercial product) with:
purity of > 99%
molecular weight: 100.16 g/mol
color: colorless
water solubility: 40 g/l (20° C)
homogeneity: homogeneous

GLP: Yes [ ] No [X]

Remarks: The duration of the entire test was 96 hours. Inoculum density was 10,000 cells/ml, test temperature was 293°K, initial pH was 9.7 and pH range was 8 to 9.7; illumination: artificial light-permanent illumination, intensity of 120 E/m2a

Reliability: [2] valid with restrictions

Reference: BASF AG. Department of Ecology, unpublished data (111 1/87), 1/22/1988.

5.0 TOXICITY

51.1 Acute Oral Toxicity

A. Preferred Result:

Type of Test: LD50

Species: Sprague-Dawley albino rats

Value: 1550 mg/kg (1390-1710 mg/kg CL)

Method: Consistent with OECD Test Guideline 40 I : single oral dose, undiluted; 2 to 3 rats/sex/dose; average weight at dosing 225 to 240 g; doses of 1000. 1260, 1580, 2000, 25 10 and 3 160 mg/kg were used

Test substance: cyclohexanol (>90% purity)

GLP: Yes [ ] No [ ] ? [X] (See Remarks)

Remarks: Most deaths occurred within 24 hours, a few within 48 hours; no deaths occurred at 1000 or 1260 mg/kg; clinical signs included weight loss, increasing weakness, ocular discharge, salivation, collapse and death. Gross autopsy results showed hemorrhagic lungs, discolored liver, and acute GI inflammation in decedents; no gross findings of toxicity were seen in survivors at 14 days. This study was conducted prior to, but was consistent with, US GLP Guidelines Published in 2 1CFR58. 1978, and effective June 20. 1979.

Reliability: [2] valid with restrictions

Reference: Younger Laboratories. Project No.Y-78-73, OTS053388617 (April 28) (TSCATS/424698), 1978.

B. Supporting Data:

Type: LD50

Species: Carworth-Wistar Rats

Value: 2060 mg/kg

Method: Single oral dose, undiluted; 5 rats/dose; _____ doses ranging from mg ik g to _____ mg/kg.

Test substance: Purity not known

GLP: Yes [ ] No [X] ? [ ]

Remarks: No additional information

Reliability: [2] valid with restrictions

Reference: H.F. Smyth et al. Am.Ind. Hyg. Assoc. J. 23: 95-107, 1962.

5.1.2 Acute Inhalation Toxicity

Type: LC50

Species: Sprague-Dawley rats (M/F)

Value: >3.63 mg/l

Method: A dynamic inhalation exposure involving head and nose was used. The dose was nominally 7.5 mg/l but was analytically determined to be 3.63 mg/l by gas chromatography. Cyclohexanol was administered as an aerosol (particle size unknown) to 10 male and 10 female rats. Body weight at the start averaged 185g ± 15g and rats were weighed 7 and 14 day after dosing.

Test substance: cyclohexanol with a purity of 99.9%

GLP: Yes [ ] No [X] ? [ ]

Remarks: No animals died during the 14-day observation period. The only clinical sign was "unkempt fur" and it occurred only during the exposure. At 14 days post-dosing, gross autopsies were unremarkable. Body weight gain was similar for control and test rats.

Reliability: [2] valid with restrictions

Reference: BASF AG, Department of Toxicology, unpublished studies (78/791), 4/19/79.

51.3 Acute Dermal Toxicity

Type: LD50

Species: New Zealand albino rabbits

Value: >501 <794 mg/kg

Method: Cyclohexanol was applied undiluted to the skin of rabbits for 24 hours, 1 male or 1 female rabbit/dose, at 7 doses ranging from 3 16 to 5010 mg/kg. Body weights ranged from 1.9 to 2.6 kg.

Test substance: cyclohexanol (> 90% purity)

GLP: Yes [ ] No [X] ? [ ]

Remarks: All deaths occurred within 24 hours. Weakness, collapse, and death. Gross autopsy of decedents showed lung hyperemia. liver and spleen discoloration, enlarged gall bladder, darkened kidneys and GI inflammation. Survivors at 14 days showed no remarkable findings at gross autopsy.

Reliability: [2] valid with restrictions

Reference: Younger Laboratories. Project No.Y-78-37, OTS0538617 (April 20). TSCATS/424698, 1978.

5.4 REPEATED DOSE TOXICITY (Inadequate Information)

Remarks:

Several limited repeated-exposure toxicity studies have been conducted by the oral route (Weitzer 1950, Lake 1982, Messiha 1985, Lox 1985,and Wakabayashi 1991), the inhalation route (Pohl 1924, DiPrisco 1932, Treon 1943, and Dobrinski 1964) and the dermal route (Pohl 1924 and Treon 1943). However, none of the preceding studies have adequate technical or scientific merit to be used to define the toxic hazard associated with repeated exposure to cyclohexanol.

Reliability: Inadequate Information

References:

- DiPrisco, L. (1932). Minerva Med. II: 432-426 (CA27:339).
- Dobrinskii, A. A. (1964). Gig. Sanit. 29 (12): 8-13 (CA62:9683f)
- Lake, B. G., et al. (1982). Acta Pharmacol. Toxicol. 51 (3): 217-226 (CA97:209833w).
- Lox, C. (1995). J. Celluar Biochem.Suppl.19A: 197 (Abstract No. A50308)(Biosis/95/15424).
- Messiha., F.S., et al. (1985). Neurobehav. Toxicol. Teratol. 7 (2): 207-208.
- Pohl, J. (1924). Z. Gewebehyg. Unfallverh. 1:91 (Cited in Treon et al. 1943).
- Treon, J. F., et al. (1943). J Ind. Hyg Toxicol. 25: 323-347 (CA39: 5002).
- Treon, J. F., et al. (1943). J Ind. Hyg Toxicol. 25: 199-214 (CA39: 5002).
- Wakabayashi. T. et al. (1991). Acta Pathol. Jpn. 41(6): 405-413 (BIOSIS/91/28271).
- Weitzel, K.G. et al. (1950). Z. Physiol. Chem. 285: 58-77 (CA44: 6527h).

5.5 GENETIC TOXICITY IN VITRO

A. Bacterial Test

(1) Type: Bacterial reverse mutation assay

System of testing: Standard plate method

Concentration: cyclohexanol concentrations ranged from 500 µg/plate to 10,000 µg/plate (without metabolic activation) or 15.000 µg/plate (with metabolic activation)

Method of Activation: With [ ] Without [ ] With and Without [X] No Data [ ]

Results: "Not mutagenic"

Test Substance: Purity unknown

Cytotoxity Concentration: 7500 µg/plate, with and without metabolic activation

Precipitation Concentration: Not applicable

Genotoxic Effects: Negative, with and without metabolic activation

Method: Four histidine-requiring strains of Salmonella *typhimurium* bacteria were used (TA 1535, TA 1537, TA 1538 and TA 98). Two replicates were used at each test substance concentration and all tests were performed in the presence and absence of a rat-liver homogenate (S.9) Approximately 10^8 bacteria were used in each plate and all plates were incubated at 37^0C for 48 hours. Both positive

(ethanol) and negative controls (2 AA, MNNG, et al.) were used in these studies.

GLP: Yes [ ] No [X] ? [ ]

Reliability: [2] valid with restrictions

Reference: DuPont Company, unpublished studies, Haskell Laboratory Report No. 755-75, **1975.**

(2) Type: Other Point Mutation Assays in Bacteria (Supporting Data)

Summary:

Three other *in vitro* studies using *Salmonella typhimurium* bacteria were conducted on cyclohexanol. In two assays (Frantz 1981; Rowe and McCollister 1982), there was no evidence of mutagenicity but details were limited. In a third study (Haworth 1983), cyclohexanol tested at 3300 µg/plate and 9100 µg/plate, with and without metabolic activation, produced results relative to mutagenicity potential.

References:

- Frantz, S.W., and J.E. Sinsheimer. Mutation Research 90: 67-78. 1981.
- S. Haworth et al: Salmonella Test Results for 250 chemicals. Environ. Mutagen. Suppl. I : 3-142. 1983.
- Rowe. V.K. and S.B. McCollister. Patty's Ind. Hyg. Toxicology, 3rd ed. pp. 4644-4649, 1982.

B. Non-Bacterial In *Vitro* Test

Type: cytogenetic assay (chromosome aberration)

System of testing: human leukocytes

Concentration: 0.01, 0.001 and 0.0001 moles/l cyclohexanol were tested

Method of Activation: With [ ] Without [X] With and Without [ ] No Data [ ]

Results: "Positive"

Cytotoxity Concentration: unknown

Precipitation Concentration: unknown

Genotoxic Effects: without metabolic activation, cyclohexanol was reported to induce achromatic regions, breaks and deletions in chromosomes.

Method: Human Leukocyte Assay described by Morhead (1960).

GLP: Yes [ ] No [X] ? [ ]

Test Substance: no data

Remarks: limited technical details; non-validated protocol; non-GLP

Reliability: [4]

References: Morhead, P.S., et al. Exper. Cell. Res. 20: 613-616, 1960.
Collins, J.P. Diabete 19 (4): 215-221, 1971 (CA77:1583u).

5.6 GENETIC TOXICITY *IN VIVO*

A. Type: Micronucleus Assay

Species/strain: NMRI Mice

Sex: Female [ ] Male [ ] Male/Female [X] No Data [ ]

Route of Administration: oral gavage

Exposure Period: 16, 24 and 48 hours for the high dose group; 24 hours for the lower doses

Doses: 500, 1000, and 1500 mg/kg bw

Results: "Negative"
Animals. receiving the positive and negative control treatments showed no signs of toxicity, but mice given cyclohexanol did have toxic signs. The frequency of erythocytes containing micronuclei was similar between negative controls and the 3 cyclohexanol dose groups (including all time points for the high-dose group).

Effect on Mitotic Index or P/N Rate: No information

Genotoxic Effects: Not an *in vivo* mutagen

Method: According to Schmid. W.: The Micronucleus Test, In: Kilbey et al. (eds.). Handbook of Mutagencity Test Procedures. Amsterdam-New York, Elsevier, 1977.
The test substance was suspended in an aqueous 0.5% carboxymethyl cellulose (CMC) formulation. It was given to male and females in a volume of IO ml/kg. The negative control received merely the carrier solution. The positive control for clastogenicity was 20 mg/kg bw of cyclophosphamide in distilled water using a volume of 10 ml/kg. The positive control for spindle poisoning effects was 0.15 mg/kg bw of vincristine in distilled water using a volume of IO ml/kg. Five males and five females were used per dose. Animals were sacrificed at the times indicated and bone marrow from both femurs was prepared. After staining, 1000 polychromatic erthrocytes were evaluated per animal and examined for micronuclei. The normocytes with and without micronuclei occurring per 1000 polychromatic erythrocytes were also recorded.

GLP: Yes [X] No [ ] ? [ ]

Test Substance: 98.8% pure cyclohexanol

Remarks: Under these experimental conditions, cyclohexanol has no chromosome-damaging (clastogenic) effects, nor does it lead to any impairment of chromosome distribution in mitosis.

Reliability: [I] valid without restrictions

Reference: BASF AG, Department of Toxicology, unpublished studies (89/843), I 0/29/9 1.

B. Type: Gene Mutation *In Vivo* (Supporting Data)

Summary: Cyclohexanol at 0.1 ml/100ml was given to *Drosophila melanogaster* (fruit flies) for 3 days as part of an SLRL Test. The results of this non-GLP test were negative, i.e, the frequency of recessive lethal mutations was not affected by treatment with cyclohexanol. even when followed by gamma and x-ray (1500R) irradiation.

Reference: R.I. Goncharova. Genetic Activity of Some Cyclohexane Derivatives. Genet. Tsito., pp. 137-142, 1970 (CA76:54780s).

5.7 TOXICITY TO REPRODUCTION

Remarks: In a study by Tyagi et al. (1979), 20 adult male gerbils and 20 male rats were subcutaneously injected with 15 mg cyclohexanol/kg/day for a period of 21 and 37 days, respectively. A significant reduction in the weights of the testes. epididymides, seminal vesicles and ventral prostate was detected. In addition, the authors indicated, based on their histological evaluation, that spermatogenesis in both species was arrested. Recovery was not investigated. In another study (Dixit et al. 1980), groups of 15 male rabbits received 25 mg cyclohexanol/kg/day by gavage for a period of 40 days. One group was allowed a 70-day recovery period following cessation of cyclohexanol administration. Similar to the preceding gerbil and rat findings, a significant reduction in the weights of the testis and epididymides was observed. Additionally, marked degenerative changes were noted upon microscopic examination of the testes. The changes were consistent with those previously described for the gerbil and the rat. Normal spermatogenesis was seen after '70 days following cessation of cyclohexanol treatment. The organ weights were also comparable to the controls. In a third study (Lake et al. 1982), male rats were given 455 mg cyclohexanol/kg/day by gastric intubation for 7 days. Cyclohexanol increased liver size and stimulated certain parameters of hepatic xenobiotic metabolism in the rat but had no effect on testis weight.

Reliability: Inadequate Information (No study meets HPV requirements.)

References:

- Dixit, V.P. et al (1980). Reversible Chemical Sterilization: Effects of Cyclohexanol Administration on the Testes and Epididmides of the Rabbits. Indian J. Physiol. Pharmacol. 24: 278-286.
- Lake, B. G. et al. (1982). Studies on the Effects of Orally Administered Dicyclohexyl Phthalate in the Rat. Acta Pharmacol. Toxicol. 5 1: 2 17-226.
- Tyagi, A, et al. (1979). Antispermatogenic Activity of Cyclohexanol in the Gerbil and House Rat. Indian Journal of Experimental Biology 17: 1305-1307.

5.8 DEVELOPMENTAL TOXICITY

No Information

5.11 EXPERIENCE WITH HUMAN EXPOSURE (WORKPLACE)

Remarks: The five US producers of cyclohexanone/cyclohexanol have, on various occasions between 1994-2000, taken area and/or personal samples for determination of possible exposure to cyclohexanol. Information has been submitted to IHF as Agent for the Consortium. To preserve the confidentiality of individual Company data, the details may be summarized as follows:

1. Samples were collected on either charcoal tubes or charcoal badges and analyzed by gas chromatography using flame ionization detection methodology.
2. The lower limits of detection varied from about 0.01 ppm for the longer-term samples (8 hours) to 0.4 ppm for short-term samples (15 minutes to one hour)
3. Area samples (n>200) and personal samples (n=200) ranged from averages of 0.01-3.5 ppm for longer sampling intervals and averages of 0.4-29 ppm for short sampling intervals.
4. Area samples tended to be of long duration with results only slightly above the appropriate detection limits for the majority of samples.
5. None of the samples taken suggested the probability of exposure in excess of the current OSHA PEL/ACGIH TLV® of 50 ppm.

Reference: Industrial Health Foundation, Pittsburgh, PA. June 15, 2001